Remarks

This is responsive to the Office Action mailed on June 23, 2005.

Claim 1 has been amended as suggested by the Examiner, to address the claim objection stated by the Examiner on page 4 of the Office Action. Applicant notes with appreciation that the Examiner has found the claim to satisfy the requirements of 35 U.S.C. 112, second paragraph. Accordingly, this amendment is not necessary for patentability, but is made to comply with the Examiner's request based on MPEP 2173.02. Based on this amendment, Applicant respectfully requests withdrawal of the objection to claim 1.

As a result, claims 1 and 52-59 are pending for examination, with claim 1 being the sole independent claim. No new matter has been added.

Rejections Under 35 U.S.C. 112, First Paragraph

A. The Examiner rejected claim 52-59 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement on the basis that these claims contain new matter. Applicant respectfully traverses the rejection.

The Examiner stated that Applicant had not provided support for the amendments to the claims. Applicant regrets any lack of showing in this respect, and provides hereinbelow exemplary support for claims 52-59 from the specification as filed. The Examiner's attention is drawn in particular to the parts that are in bold and underlined text.

Regarding support for claims 52, 55 and 58, the Examiner's attention is directed to page 29, lines 5-14, which states (emphasis added):

> "Instead of constructing an RRF inhibitor from one fragment or chemical entity at a time in a stepwise manner as described above, the inhibitory compound

or other **RRF bound compound can be designed wholly or anew** by use of the active site (or one containing some parts of a known inhibitor as needed) from the RRF. As these methods there can be cited the followings:

The following program is available from Biosym Technologies, San Diego, CA: LUDI (Bohm, H. J., "The Computer Program LUDI: "A New Method for the **de novo Design** of Enzyme Inhibitors", J. Comp, Aid, Molec, Design, 6 pp. 61-78(1992)."

Thus, the recitation in claims 52, 55 and 58 of a "compound capable of binding to RRF protein is designed de novo" is fully supported in the specification as filed.

Regarding support for claims 53, 56 and 59, the Examiner's attention is directed to page 22, line 24 – page 23, line 6, which states:

"Another approach that is made possible and facilitated by the present invention is to perform screening by use of a computer on a chemical entity or compound that can bind to RRF entirely or partially. In this screening, the property of conformity of such a chemical entity or compound to the binding site can be judged by either shape complementarity or estimated interaction energy (Meng, E.C. et al. J. Comp. Chem., 13, 505-524 (1992))."

The Examiner's attention is also directed to page 29, lines 5-9, which states (emphasis added):

"Instead of constructing an RRF inhibitor from one fragment or chemical entity at a time in a stepwise manner as described above, the inhibitory compound or other RRF bound compound can be designed wholly or anew by use of the active site (**or one containing some parts of a known inhibitor as needed**) from the RRF."

Thus, the recitation in claims 53, 56 and 59 of a "compound capable of binding to RRF protein is designed from a known compound capable of binding to RRF protein" is fully supported in the specification as filed.

Regarding support for claim 54, the Examiner's attention is directed to page 21, lines 12-17, which states (emphasis added):

> "The present invention for the first time makes it possible to use a molecular design technology in which chemical entity and compound are designed, selected and **synthesized** with respect to RRF. The chemical entity and compound include inhibitory compounds that can bind to all or a portion of the active site or accessory-binding site of RRF."

The Examiner's attention is also directed to page 24, lines 19-21, which states (emphasis added):

> "Therefore, the data can be used for optimizing an RRF inhibitor and more importantly, can be used for designing a novel RRF inhibitor **and synthesize it**."

Thus, the recitation in claim 54 of "b) synthesizing said compound capable of binding to RRF protein" is fully supported in the specification as filed.

Regarding support for claim 57, the Examiner's attention is directed to page 26, lines 3-8, which states (emphasis added):

> "...in the case where the computer modeling suggests strong interaction, the molecule can be synthesized and its inhibitory capability can be tested by the method of Hirashima and Kaji (Biochemistry, 11, 4037 (1972)) or a method using an oligonucleotide, and in vivo screening (Japanese Patent Application No. Hei 10-158643)."

Thus, the recitation in claim 57 of "c) contacting said compound capable of binding to RRF protein with said RRF protein in the presence of a substrate to determine the ability of said compound capable of binding to RRF protein to bind said RRF protein" is fully supported in the specification as filed.

B. The Examiner rejected claims 1 and 52-59 under 35 U.S.C. 112, first paragraph, as not enabled. Applicant respectfully traverses the rejection.

The Examiner suggests that the specification does not provide working examples, and consequently the practice of the invention would be unpredictable. The Examiner also suggests that one of the factors affecting the predictability of the practice of the invention is that structure of RRF determined by Applicant is that of an unliganded protein, and further that the active site of RRF is not definitively identified (page 9 of the Office Action).

Applicant respectfully disagrees for at least the following reasons. The specification identifies the active site of RRF as including Arg 110, Arg 129 and Arg 132 of SEQ ID NO:1 (see page 11, lines 15-17, page 17, lines 15-20, and page 21, lines 4-11). In addition, the description of Figure 3 on page 20 of the specification also describes the active site in the context of a ribbon diagram of the RRF protein as deduced from the crystallographic data. Applicant has, therefore, provided the skilled person with a description of the RRF protein structure and active site, including the identification of amino acid residues that likely are present in the active site, and a more general identification of the active site as shown in the ribbon diagram of the protein. Mutational studies (see below) further support that Arg 110, Arg 129 and Arg 132 are active site residues. These teachings provide more than adequate teachings for one of ordinary skill in the art to practice the claimed invention without undue experimentation.

Applicant respectfully disagrees that no working examples were provided that confirm the active site residues. Applicant performed mutational studies that confirmed that Arg 110, Arg 129 and Arg 132 are active site residues. See Example 3, part 2 ("Presumption of the active

site of RRF"), on pages 45-50. Briefly, Applicant induced mutations in the RRF coding sequence using error-prone PCR, obtaining 61 mutant strains that had a mutation that rendered RRF non-functional (described as a "lethal mutation") by the selection procedure described in the Example. That the lethal gene alleles did not encode active RRF was confirmed by use of *E. coli* strain LJ4, which has a temperature-sensitive RRF (Janosi et al., EMBO J. 17:1141 (1998)). All the obtained plasmids carrying mutant RRF alleles were not able to support the growth of LJ4 at 42°C. These mutant RRF-encoding sequences had 53 different genotypes, which are listed in Table 5. As shown in Table 5, more than half of the mutants having a single amino acid change had a change at one of Arg110, Arg129 or Arg 132.

Thus, Applicant has clearly provided working examples confirming the presence of Arg110, Arg129 and Arg 132 in the active site of RRF.

Applicant notes that in contrast, in the Wilson patent cited by the Examiner, only 15 mutations are shown to suggest the residues of Interleukin-1β converting enzyme (ICE) that form active site (Example 2 and Fig 3).

It is clearly stated in a later publication by Applicant and collaborators (Janosi L. et al., J. Mol. Biol. 295: 815-829 (2000)) that mutations near Arg132 do not influence the overall structure of RRF (see page 825, left column, line 7 to last). It is extremely important that the null mutation may or may not be caused due to the change of the particular residues. It is well known among skilled persons in the art that null mutations can be caused by structural change of entire molecule and are not necessarily due to the change of the active site. The Wilson patent does not provide this information.

As further evidence of the ability of one of ordinary skill in the art to practice the claimed invention, Applicant provides herewith several literature references that demonstrate that the active site does in fact include the amino acid residues that Applicant disclosed in this application. Further the references show that the RRF protein active site binds to the ribosome, which implies an interaction that can be inhibited with compounds binding the RRF active site, thereby inhibiting the recycling of the ribosome.

The references are Wilson et al., EMBO J. 24:251-260, 2005; Agrawal et al., Proc. Natl. Acad. Sci USA 101:8900-8905, 2004; Lancaster et al., Cell 111:129-140, 2002; and Gao et al., Molecular Cell 18:663-674, 2005.

Wilson et al. shows that Arg129 and Arg132 are involved in the binding of RRF to the ribosome. In particular, Figure 4 shows the position of these residues and the interacting parts of the ribosome. On page 255, Wilson et al. state that "...Arg129 can form hydrogen bonds with the ribose O2' of G1945 [on the rRNA]...In addition to the interactions with the backbone of the rRNA, base-specific interactions are seen for Arg132 (NH2) ...." This demonstrates that these two residues of RRF have important contacts with the ribosome.

Wilson et al. then stated on page 255: "Many of these interactions are likely to be used for the binding of RRF from other species to their respective ribosomes, since Glu122, Arg129 and Arg132 are universally conserved within all RRF sequences known to date...."

The Agrawal et al. reference also supports the importance of the residues identified by Applicant. The authors stated on pages 8902-8903 that "In RRF, the α-helix 5 segment, encompassing amino acid residues 122-133 within domain I...appear to form the most stable connection with the ribosome...."

Likewise, the Gao et al. reference stated on page 665 that "Consistent with the previous cryo-EM data (Agrawal et al., 2004), the most distinct contact of RRF with the 50S subunit are formed between the α-helical bundle tail of RRF and both H69 and H71. Specifically, RRF residues Glu120-Arg133 of α helix 3 (Kim et al., 2000) are located at the groove formed by H69 and H71 and strongly interact with both helices."

These results presented by the independent papers published as stated above have already been predicted by the pioneering work by Lancaster et al. (Cell 111:129-140, 2002). On page 135 of this reference, one of inventors, Dr. Kaji, and his collaborators stated "RRF most closely approaches nucleotides 1942-1947 and 1963-1965 of helix 71 and 1907-1908 of helix 69 at its

universally conserved residues R129 and R132 (mutations which confer lethal phenotypes; Janosi et al., 2000), E122, and the highly conserved N130, R133, K144, and Q161, all located in domain I." (see also Figure 6 (A) and (B)). The above cited mutational studies are a part of the present specification as shown in Table 5 and as described above.

Thus, the results described in the specification and in the published references provided herewith support the predictability of the practice of the invention. These references show that Applicant's determination of the active site was definitive; this information clearly is usable by one of ordinary skill in the art in identifying compounds that bind to RRF and disrupt binding of RRF to the ribosome.

Moreover, Applicant has provided complete protein crystallographic coordinates of RRF (Table 8), which can be used by one of ordinary skill in the art to generate additional structural models of the RRF protein using only routine experimentation. This appears to have been acknowledged by the Examiner in that the Examiner recognized that a person of skill in the art can readily utilize such data (e.g., as described in the Wilson patent).

It must be kept in mind that the person of skill in this particular art is highly skilled. Thus, the identification by Applicant of the crystal structure, the active site, and even specific amino acid residues present in the active site is sufficient for the skilled person to carry out the claimed methods. In addition, on page 3, the specification describes the process as known in the art and carried out on HIV protease. Thus it is clear that the skilled person is aware of the techniques and methods used in carrying out the claimed invention.

Rejections Under 35 U.S.C. § 103

The Examiner rejected claims 1 and 52-59 under 35 U.S.C. § 103 as unpatentable over US patent 5,856,116 (Wilson et al.) in view of In re Gulack, 703 F.2d 1381, 217 USPQ 401 (CAFC 1983). Applicant respectfully traverses the rejection and requests reconsideration.

According to the Examiner, the Wilson patent teaches methods for designing and selecting compounds that bind to an enzyme using a three-dimensional model of the enzyme. The Examiner asserts that the Wilson method is the same as the presently claimed method, while missing only the specific structural coordinates provided in Table 8 of the instant specification. The Examiner also asserts that this difference is "limited to descriptive material stored on or employed by a machine.

The Examiner then asserts that the court in In re Gulack held that "nonfunctional descriptive material in a claim does not distinguish the prior art in terms of patentability." Office Action at page 11. The Examiner then finds that "the RRF structural coordinates as disclosed in Table 8 are non-functional descriptive material and the method uses a known unmodified computer algorithm." Id.

The Examiner's conclusion that the claimed invention is obvious is based on the unwarranted conclusion that the RRF structural coordinates are "non-functional descriptive material". The conclusion is also based on an erroneous application of the holding of In re Gulack. For each of these reasons, the finding that the claimed invention is unpatentable as obvious over the Wilson patent is incorrect.

The Examiner merely asserts that the structural coordinates are "non-functional descriptive" material. This is plainly incorrect. To a person of skill in the art, the structural coordinates clearly are not merely descriptive material, particularly not in the sense referenced by the court in In re Gulack.

The Gulack court in fact supported the ability of printed matter to distinguish a claimed invention from the prior art. The court stated: "Differences between an invention and the prior art cited against it cannot be ignored merely because those difference reside in the content of the printed matter." Gulack at 1385, 217 USPQ at 403, emphasis added.

In footnote 8, the court elaborated on this point and the long history of cases on point:

> "A 'printed matter rejection' stands under § 103 stands on questionable legal and logical footing. Standing alone, the description of an element of the invention as printed matter tells nothing about the difference between the invention and the prior art or about whether that invention was suggested by the prior art. A printed matter rejection is based on case law antedating the 1952 patent act....The CCPA has considered *all* of the limitations of the claims including the printed matter limitations, in determining whether the invention would have been obvious. See In re Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974)....In Royka, 490 F.2d at 985, 180 USPQ at 583, the CCPA, notably weary of reiterating this point, clearly stated that printed matter may well constitute structural limitations upon which patentability can be predicated." Gulack at 1388, 217 USPQ at 406, italics in original, underlining added.

In the specific instance dealt with by the court in Gulack, the printed matter of the prior art was data that bore "no direct relation to the other data entries...The relationship of the Wittcoff [prior art] data to the band [prior art device] is for purposes of support and display." Gulack at 1386, 217 USPQ at 405. In contrast, the printed matter in the Gulack application were related to the band in two ways: the band supported the digits, and each digit resided in an unique position with respect to the other digits in the endless loop. Gulack at 1386-7, 217 USPQ at 405. The Gulack court concluded that the claimed features were critical to the invention disclosed by the appealed claims. Gulack at 1387, 217 USPQ at 405.

Similarly, a functional relationship exists between Applicant's data provided in Table 8 and the other elements of the claimed invention. The claims recite methods for identifying a compound capable of binding to ribosome recycling factor (RRF) protein, in which the three-dimensional structure of RRF is defined by atomic coordinates of RRF protein provided in Table 8. The method is used to design or select compounds capable of binding to RRF protein. Thus the data is functional, because without it one of skill in the art could not practice the claimed invention given the teachings of the prior art.

Moreover, the claims do not represent a mere use of a "known comparator for its known purpose to compare data sets" as asserted by the Examiner. The claimed method utilizes the structural data to construct a three dimensional structure of the RRF protein, which then is used in identifying compounds that bind to RRF.

Under the principle confirmed in Gulack, functional data such as that in Table 8 must be considered in the analysis of obviousness, because it is part of the claimed invention that must be considered "as a whole". 35 U.S.C. 103. Applicant takes the view that the Examiner did not consider fully the claimed invention as a whole, and therefore did not appreciate the functional relationship between the Table 8 data and the remaining elements of the claimed invention.

Applicant also disagrees with the Examiner's determination that the data provided in Table 8 is non-functional. The Examiner arrives at this viewpoint by categorizing the claimed invention and the data in terms of an algorithm, and suggests that to be functional, data must "impose a change in the processing steps." Office Action at page 12. Applicant disagrees with this characterization because the nature of the claimed invention is different than that stated by the Examiner. The purpose of the data in Table 8 is not *per se* to impose a change in processing steps; rather, the data provides a description, when a proper algorithm is used, of the three-dimensional structure of the RRF protein. The claimed invention is the use of that structure in designing or selecting compounds that bind to the protein.

To illustrate that the use of a protein structure as defined by atomic coordinates is an important and patentable entity, Applicant gives the following analogy. In an organic synthesis reaction, the starting material defines the final product even if one uses a known routine method of synthesis. For example, one can convert compound A, a ketone, to compound B, an alcohol, using a reduction reaction. A new ketone compound, X, also can be converted to an alcohol (compound Y) using the same reduction reaction. Likewise, software such as LUDI is used to "convert" atomic coordinates to protein structure. The software program is the equivalent of the reduction reaction method in the analogy provided above, while the structural information such as in Table 8 of the present invention corresponds to the starting material (ketone) in the analogy.

As additional evidence that the use of a protein structure as defined by atomic coordinates is indeed patentable, US patents have been granted to the use of structural information of a known protein. Three examples of such patents are: US 6,183,121, US 6,303,287 and US 6,387,641. In all of these patents, the intention is the same as the present invention; use of patented structural information to device new compounds which binds to the protein using

known computer algorithm. The claims of these patents reflect this intention, such as claim 16 of US 6,183,121, which recites: "using the atomic coordinates ... to generate a three-dimensional structure" of a particular protein molecule, and "employing said three-dimensional structure to design or select said potential agonist or antagonist".

Accordingly, in view of the foregoing, Applicant respectfully requests reconsideration and withdrawal of the rejection of the claims as unpatentable over US patent 5,856,116 (Wilson et al.) in view of In re Gulack.

CONCLUSION

In view of the foregoing amendments and arguments, this application should now be in condition for allowance. A notice to this effect is respectfully requested. If the Examiner believes, after this amendment, that the application is not in condition for allowance, the Examiner is requested to call the Applicant's attorney at the telephone number listed below.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,
Kaji, et al., Applicant

By: _____

John R. Van Amsterdam, Reg. No. 40,212
Wolf, Greenfield & Sacks, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210-2211
Telephone: (617) 646-8000

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